REMARKS

I. Status of Application

Claims 50, 57, 61, and 62 are pending in the application. Claims 1-4, 6-49, and 51-56 were previously canceled and claims 5, 58-60, and 64-69 were withdrawn. By way of the present response, claims 50 and 57 have been amended and claim 63 has been cancelled. Support for the amendments can be found throughout the specification as filed. No new matter has been added.

II. Claim Rejections Under 35 U.S.C. § 103

Nienaber in view of Dauter as evidenced by Wlodawer

Claims 50, 57, and 63 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Nienaber *et al.* (Nature Biotechnology 18: 1105-1108 (2000)), in view of Dauter *et al.* (Acta Crystallographica D57:239-249 (2001)), as evidenced by Wlodawer *et al.* (Nature Structural Biology 8(5): 442-446). Specifically, the Examiner states that Nienaber teaches a method for screening a library of candidate compounds having binding affinity towards a given target biomolecule as a mean towards developing a lead compound that has optimized binding properties. The Examiner further states that the method Nienaber relies upon utilizes x-ray crystallography for making structural determinations, namely by monitoring changes in the electron density of the biological target in the free and ligand-bound state. Further, the Examiner acknowledges that Nienaber does not explicitly teach that the crystal having the biomolecule and ligand also comprises a second compound having anomalous dispersion properties, as in step 'a' of claim 50. Applicant respectfully traverses this rejection.

(1) Skilled artisans would not have combined Neinaber *et al.*, Dauter *et al.*, and/or Wlodawer *et al.*

Under, *KSR International Co. v. Teleflex Inc.*, the United States Supreme Court has noted that the analysis supporting an obviousness rejection under 35 U.S.C §103 should be made explicit. 127 S. Ct. 1727, 82 USPQ2d 1385, 1396 (2007). Moreover, one of skill in the art must have had some motivation to combine the references in the manner necessary to arrive at the claimed invention. Further, the prior art can only be modified or combined to reject claims as prima facie obvious when

there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant respectfully submits that the references cited by Examiner do not render obvious the claims pending in the instant application.

A. Nienaber et al.

Nienaber teaches a screening method using specially designed mixtures which are shape-diverse. For example, Nienaber teaches that:

> To increase the sampling rate of the crystallographic screening method, compounds are tested as specially designed mixtures. These mixtures are designed to capitalize on the high-resolution structural data available from X-ray crystallography. Specifically, the raw experimental data (electron density map) provides the shape of the bound compound and can therefore provide the identity of the ligand in a mixture if the mixture is suitably designed to be shape-diverse. Testing of mixtures of differently shaped compounds permits direct identification of the bound molecule from the primary data (electron density map) and virtually eliminates the need for time-consuming and sometimes technically difficult deconvolution experiments.

Nienaber *et al.*, at 1106 (emphasis added). Further, Nienaber describes a previously performed experiment for the purpose of studying inhibitor binding to a "selectivity region of triosephosphate isomerase." *Id.* Nienaber concludes that while this experiment gave an electron density map different from the native uncomplexed crystal, the identification of the ligand was not determined because of low resolution and "the mixture was not designed to be shape-diverse." *Id.* (emphasis added).

Given the disclosure above, Nienaber would not have rendered obvious the instant claims, which require the step of combining a crystalline biological target molecule with a mixture comprising at least two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine. Rather, Nienaber solely taught the use of mixtures that were shape-diverse and emphasized the importance of using diverse shapes.

B. Dauter et al.

Dauter does not cure the defects of Nienaber and does not render obvious, alone or in combination with Nienaber, methods for designing a lead candidate by combining a crystalline biological target molecule with a mixture comprising at least two compounds, wherein at least one of the

compounds comprises a substituent having anomalous dispersion properties comprising bromine, as required by the instant claims. Rather, Dauter (i) teaches an elucidation of a crystal structure of an enzyme known as pepstatin-insensitive carboxyl proteinase (PCP) from *Pseudomonas* sp. 101; and (ii) discusses "the practical aspects of solving the crystal structure of PCP and analyze[s] both the successful experiments and the failed ones that utilized different crystal forms." Dauter *et al.*, at 240 (emphasis added). Additionally, Dauter's purpose in solving the structure of PCP was to validate a solution to the phase problem for proteins with unknown folds. *Id.* at 239.

A skilled artisan, given the goal of solving phase problems of proteins with unknown folds as taught in Dauter, would not combine Dauter with Nienaber with any reasonable expectation of success. Dauter states that "[t]he traditional method of solving the phase problem for proteins with unknown fold has been multiple isomorphous replacement (MIR) and its several variants. . . In this approach, protein crystals are derivatized by soaking in solutions of heavy atoms, usually metal salts or organometallic compounds." *Id.* Emphasizing the difficulty of derivatizing protein crystals for solving phase problems, Dauter goes on to state that "[t]he choice of proper derivatives is heuristic and very dependent on the nature of the protein under study and thus not easy to generalize," thereby acknowledging the complexity associated with protein crystal derivatization. *Id.* at 240. Such a complex and heuristic approach would not teach or suggest to a skilled artisan that combining protein crystal derivatization for solving phase problems for proteins with unknown folds (Dauter) and shape-diverse mixtures (Nienaber) would produce the instant claims. Nor has the Examiner pointed to any reason one of skill in the art would have made this combination.

C. Wlodawer et al.

Wlodawer also does not cure the defects of Nienaber. Similar to Dauter, Wlodawer teaches the elucidation of the crystal structure of pepstatin-insensitive carboxyl proteinase from *Pseudomonas* sp. 101. It does not, alone or in combination with any other references relied on by the Examiner, render obvious the methods for designing a lead candidate by combining a crystalline biological target molecule with a mixture comprising at least two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine, as required by the instant claims. Applicant respectfully maintains that Wlodawer adds nothing new to Dauter. Thus,

Applicant respectfully requests reconsideration and withdrawal of the rejection based on the arguments made above.

(2) Not all claim limitations are taught or suggested by Nienaber, Dauter or Wlodawer

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); MPEP §2143.03. "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA) 1970.

Amended claim 50 reads as follows:

> A method of designing a lead candidate having biophysical or biochemical activity against a biological target molecule, comprising the steps of:
>
> a) Combining a crystalline biological target molecule with a mixture comprising at least two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine;
>
> b) Determining the structure of at least one of the compounds in association with the biological target molecule using x-ray crystallographic analysis; and
>
> c) Selecting information from the structure to design the lead candidate.

Amended claim 57 reads as follows:

> The method of claim 50, wherein determining the structure of at least one compound of step b uses the anomalous dispersion properties of the substituent.

Applicant respectfully submits that Examiner has not established that claim 50 is prima facie obvious in view of the references relied on by the Examiner because at least one limitation of claim 50, i.e., a mixture comprising at least two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine," is not taught or suggested by any of these references.

As discussed above, Nienaber teaches that "[t]he crystallographic screening method is initiated by exposing the crystal to a mixture of diversely shaped compounds." Nienaber et al., p. 1105 (emphasis added). In contrast, claim 50 is not directed to a mixture of diversely shaped compounds, but rather a mixture comprising at least two compounds wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine.

Similarly, Dauter teaches a crystal "in the form of [a] complex[] with either a specific inhibitor tyrostatin or its iodinated derivative," such that the specific inhibitor and the proteinase have been crystallized as a complex. Dauter et al., p. 240 (emphasis added). Also, Wlodawer teaches that "[a]ll crystals were grown from a solution containing a mixture of PSCP with the inhibitor iodotryostatin." Wlodawer et al., at 446 (emphasis added). Pending claim 50, on the other hand, is directed to a mixture comprising at least two compounds wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine.

Because the references cited by Examiner do not teach or even suggest all of the elements disclosed in claim 50, or dependent claim 57, Applicant respectfully requests that Examiner withdraw this rejection.

Nienaber in view of Dauter as evidenced by Wlodawer and in view of Reddy

Claims 50, 57, 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nienaber *et al.* (Nature Biotechnology 18:1105-1108 (2000)), in view of Dauter *et al.* (Acta Crystallographica D57:239-249 (2001)), as evidenced by Wlodawer *et al.* (Nature Structural Biology 8(5):442-446), and in view of Reddy *et al.* (JACS 123:6246-6252 2001)). Specifically, the examiner states that:

> One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Nienaber, Dauter and Wlodawer, are directed to the use of x-ray crystallography for structural analysis of protein-substrate interactions. One of ordinary skill in the art would have been motivated to utilize the improved x-ray technique and advances presented by Dauter, which are consistent for high-throughput screening, as in Nienaber for developing lead compounds based on the x-ray data obtained by screening a library of compound having binding affinity to a given biomolecule. Therefore the invention as a whole was *prima facie* obvious at the time it was invented.
>
> The further modification of the method of Nienaber and Dauter by Reddy would be a recognized advantage because of the accelerated pace and experimental confidence that established molecular dynamics simulations provide in lead compound development, especially considering that claim 50 reads on Nienaber and Reddy to the same extent. Therefore the invention as whole was *prima facie* obvious at the time it was invented.

Applicant also traverses this rejection.

(1) One of skill in the art would not have combined Neinaber *et al.*, Dauter *et al.*, Wlodawer *et al.* and/or Reddy *et al.*

For the reasons given previously, Applicant respectfully submits that based on the teachings in Nienaber, Dauter, and Wlodawer one of skill in the art would have not motivation to combine the

references so as to arrive at the claimed invention. Nienaber teaches a screening method using specially designed, shape-diverse mixtures. Dauter teaches an elucidation of a crystal structure of an enzyme known as pepstatin-insensitive carboxyl proteinase from *Pseudomonas* sp. 101 as well as validating a solution to the phase problem for proteins of unknown folds. Wlodawer, similar to Dauter, teaches the elucidation of the crystal structure of pepstatin-insensitive carboxyl proteinase from *Pseudomonas* sp. 101. One of skill in the art at the time of the invention would not have combined these references to arrive at a method for designing a lead candidate as required in the instant claims given these teachings. Applicant respectfully requests Examiner to reconsider and withdraw this rejection.

B. Reddy et al.

Reddy also does not cure the defect of Nienaber. Similar to Dauter and Wlodawer, Reddy teaches "crystallographic structure determination of protein-inhibitor complexes" and not a method of designing a lead candidate comprising combining a crystalline biological target molecule with a mixture comprising at least two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine, as required by the instant claims. Applicant respectfully asserts that because claims 61 and 62 ultimately depend from claim 50, and claim 50 is not obvious in light of the arguments presented above, claims 61 and 62 are also not obvious. Claim 63 has been cancelled rendering this rejection moot.

For at least the foregoing reasons, Applicant respectfully requests that this rejection be withdrawn. Allowance of the pending claims is earnestly solicited.

CONCLUSION

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 20268-705.201). Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (858) 350-2319.

Respectfully submitted,

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